ECHOCARDIOGRAPHIC ASSESMENT OF LEFT ATRIAL APPENDAGE FUNCTION IN PATIENTS WITH MITRAL STENOSIS BY TISSUE DOPPLER VELOCITY IMAGING

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"learn to heal"

CERTIFICATE

This is to certify that the dissertation entitled **"EHOCARDIOGRAPHIC ASSESMENT OF LEFT ATRIAL APPENDAGE FUNCTION IN PATIENTS WITH MITRAL STENOSIS BY TISSUE DOPPLER VELOCITY IMAGING"** is a bonafide original work of **DR.D.RAJASEKHAR RAMESH** in partial fulfillment of the requirements for D.M. Branch-II (CARDIOLOGY) examination of THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY to be held in August 2009.The period of post-graduate study and training was from August 2006 to July 2009.

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DECLARATION

I, **Dr.D.RAJASEKHAR RAMESH,** solemnly declare that this dissertation entitled, **"EHOCARDIOGRAPHIC ASSESMENT OF LEFT ATRIAL APPENDAGE FUNCTION IN PATIENTS WITH MITRAL STENOSIS BY TISSUE DOPPLER VELOCITY IMAGING"** is a bonafide work done by me at the department of Cardiology, Madras Medical College and Government General Hospital during the period 2006 – 2009 under the guidance and supervision of the Professor and Head of the department of Cardiology of Madras Medical College and Government General Hospital, Professor **R.Subrammanian;M.D.D.M.** This dissertation is submitted to The Tamil Nadu Dr.M.G.R Medical University, towards partial fulfillment of requirement for the award of **D.M. Degree (Branch-II) in Cardiology.**

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D.RAJASEKHAR RAMESH

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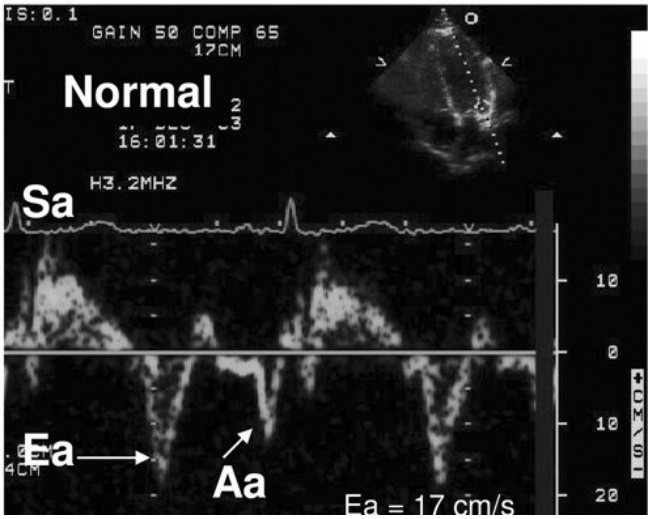
CONTENTS

Introduction

Rheumatic heart disease is one of the commonest cardiac conditions in India in both children and adults, accounting for 30 - 40% of cardiac cases admitted in hospital. Approximately 25% of all patients with rheumatic heart disease have pure or predominant mitral stenosis (MS).
Thromboembolism develops in atleast 20% of mitral stenosis patients, at sometime during the course of their disease. Thromboembolism remains an important cause of morbidity and mortality in rheumatic MS.
Echocardiography is the widely used method for detecting left atrial and left atrial appendage thrombi. Trans thoracic echocardiography (TTE) is only 50% sensitive in detecting LA and LAA thrombi.Transesophageal echocardiography (TEE) is 99% sensitive and specific in detecting LA and LAA thrombi.
Echocardiography when combined with spectral and colour flow Doppler is well established as a safe, non-invasive, and versatile diagnostic modality in cardiology, and is now the predominant technique used for evaluation of left ventricular function and for the assessment and quantification of valvar heart lesions. When combined with physiological or pharmacological stress, echocardiography also enables the identification of reversible myocardial ischaemia and myocardial contractile reserve. However, assessment of regional cardiac dysfunction at rest and during stress remains subjective and semiquantitative, with high interobserver variability. Doppler measurement of myocardial motion,using pulsed wave Doppler, was first proposed in 1989 but this technique allowed realtime visualisation of only a single myocardial segment and its potential was not realised.Only later, with the development of colour flow algorithms to visualise myocardial motion,did the technique begin to gain clinical acceptability.
Subsequent software development has led to improved temporal and spatial resolution and off line processing to enable quantification of multiple segments of myocardium in seconds. These technological advances have been matched by widespread clinical interest in the technique and an explosion of clinical research.
Tissue Doppler imaging (TDI) is a relatively new echocardiographic technique that uses Doppler principles to measure the velocity of myocardial motion.
Doppler echocardiography relies on detection of the shift in frequency of ultrasound signals reflected from moving objects. With this principle, conventional Doppler technique assess the velocity of blood flow by measuring high-frequency, low-amplitude signals from small, fast-moving blood cells. In TDI, the same Doppler principles are used to quantify the higher-amplitude, lower-velocity signals of myocardial tissue motion.
There are important limitations to TD interrogation. As with all Doppler techniques, TDI measures only the vector of motion that is parallel to the direction of the ultrasound beam. In addition, TDI measures absolute tissue velocity and is unable to discriminate passive motion (related to translation or tethering) from active motion (fiber shortening or lengthening). The emerging technology of Doppler strain imaging provides a means to differentiate true contractility from passive myocardial motion by looking at relative changes in tissue velocity.
TDI can be performed in pulsed-wave and color modes. Pulsed-wave TDI is used to measure peak myocardial velocities and is particularly well suited to the measurement of long-axis ventricular motion because the longitudinally oriented endocardial fibers are most parallel to the ultrasound beam in the apical views. Because the apex remains relatively stationary throughout the cardiac cycle, mitral annular motion is a good surrogate measure of overall longitudinal left ventricular (LV) contraction and relaxation.
To measure longitudinal myocardial velocities, the sample volume is placed in the ventricular myocardium immediately adjacent to the mitral annulus. The cardiac cycle is represented by 3 waveforms (1) Sa, systolic myocardial velocity above the baseline as the annulus descends toward the

apex; (2) Ea, early diastolic myocardial relaxation velocity below the baseline as the annulus ascends away from the apex; and (3) Aa, myocardial velocity associated with atrial contraction. The lower-case "a" for annulus or "m" for myocardial (Ea or Em) and the superscripted prime symbol (E') are used to differentiate tissue Doppler velocities from conventional mitral inflow. Pulsed-wave TDI has high temporal resolution but does not permit simultaneous analysis of multiple myocardial segments.



The incidence of systemic embolism remains high in patients with mitral stenosis (MS). The left atrial appendage (LAA) is a potential site for the development of thrombus. Normally this highly dynamic structure prevents stasis.

However, decreased contractility of the LAA is associated with the development of spontaneous echo contrast (SEC) and thrombus. It has been shown that the LAA dysfunction is an independent predictor of thromboembolic event

AIM OF THE STUDY

The most widely accepted method for assessing the left atrial appendage (LAA) function is the measurement of left atrial appendage late peak emptying velocity (LAAEV) by using pulse wave Doppler (PWD) on Transesophageal echocardiography (TEE) and reduced left atrial appendage late peak emptying velocity represents left atrial appendage dysfunction. The magnitude and pattern of left atrial appendage flow velocities are dependent on acute changes in loading conditions. Left atrial appendage flow velocities may also be affected by left atrial appendage size and morphology which are highly variable.

Myocardial velocities obtained by Tissue Doppler imaging (TDI) are less dependent on preload and left atrial appendage (LAA) tissue velocities may help in more accurate risk prediction.

The aim of the study is to

(1) To asses Left Atrial appendage late peak Emptying Velocty (LAAEV) and Left Atrial appendage late peak Filling flow Velocty (LAAFV) by using Pulse Doppler imaging in Trans esophageal echocardiography (TEE)

(2) To asses Left Atrial appendage late peak Systolic tissue velocity (LSV) and Left Atrial appendage late peak Diastolic Velocty (LDV) by using Tissue Doppler imaging in Trans esophageal echocardiography (TEE)

(3) To correlate left atrial Spontaneous Echo Contrast (SEC) and thrombus with Left Atrial appendage late peak Systolic tissue velocity (LSV) and Left Atrial appendage late peak Emptying Velocty (LAAEV)

BACKGROUND

Rheumatic heart disease remains one of the commonest acquired heart diseases affecting young and middle aged population in our country.
Pure or predominant Mitral stenosis (MS) is the commonest presenting manifestation of chronic rheumatic heart disease accounting for 40 percentages of all cases.
Females outnumber males and affected more commonly by rheumatic MS.
Left atrial thrombus formation is an important complication of rheumatic MS causing morbidity and mortality.
In one study 17% of patients undergoing surgery for mitral stenosis have left atrial thrombus and in about two third of these patients, the thrombus is restricted to left atrial appendage (LAA).
Deveral et al reported that 16% of patients evaluated for MS had a history of systemic embolism.
In approximately 10-15% of patients with MS systemic embolic manifestation due to left atrial thrombus may be the first symptom. Cerebral embolism constitutes 60-70 % of episodes of systemic embolism in several series.
Emboli are often fatal in patients with mitral stenosis. In a 10 year follow-up of 250 patients with unoperated MS, Rowe et al, found that 9% of 110 deaths in the first 10 years of follow-up are due to systemic embolism. In the follow-up series of Olesen, 22% of all deaths in MS were due to thromboembolism.
Several studies reported that the following factors are associated with left atrial thrombus formation in MS

- Atrial fibrillation
- Age-Higher the age, greater the risk.
- Left atrial size.
- Left atrial spontaneous echo contrast.
- LV systolic dysfunction

The severity of mitral stenosis does not correlate with risk of thrombus formation.
On the other hand presence of significant mitral regurgitation is a negative predictor of development of left atrial thrombus .This may be due to an increase in flow velocity with in left atrium in systole created by MR.
In the classical series of Coulshed et al, 737 patients with predominant mitral stenosis were followed up for cardiac events. Of 248 patients of 35 years or less, the incidence of embolisation was 9% .Of 489 patients over 35 years, the incidence was 24%.
Deveral et al, found that incidence of systemic emboli correlates better with years since initial rheumatic activity than chronological age per se.

ATRIAL FIBRILLATION (AF)

Atrial fibrillation is another important factor associated with left atrial thrombus Most of the MS patients who have systemic embolism are in AF. The prevalence of AF increases with age.
Eighty percent of patients with MS, in whom systemic emboli develop, are in atrial fibrillation (AF).
The combination of MS and AF, increases the chances of stroke 17 fold.
There is a 7 times greater risk of stroke in patients with MS in AF, when compared with those with MS in sinus rhythm (SR). Just the presence of MS and AF, is said to confer the greatest risk for thromboembolism.
In coulshed et al series, in those over 35 years of age, the incidence of systemic embolism was 32% in those with AF as against 11% in those in sinus rhythm.
When atrial fibrillation supervenes, blood flow in the atrial appendage and in the body of the left atrium becomes more disorganised, with low velocity, multidirectional flow patterns, blood flow stasis, and development of atrial thrombi.
This swirling pattern of low velocity flow often is evident as spontaneous echo contrast in

echocardiography, particularly when using a high frequency transducer from transesophageal approach.

LEFT ATRIAL SIZE

Left atrial size is assessed by various methods most commonly left atrial dimension measured by M-mode in transthorasic parasternal long axis (PLAX) at the level of aortic valve level. The measurement is made at end-systole, just before mitral valve opening when the left atrial volume is maximal.
In addition various studies indicated that left atrial volume is a powerful prognostic factor in variety of situations
Left atrial dimensions were measured in end systole in PLAX-antero posterior and two orthogonal diameters in four chamber view and left atrial volume calculated by using prolate ellipse method.

Left atrial volume = (Dl X D2 X 03) X 0.523

In patients with MS in SR, LA size correlates with the development of AF, and it said that those with LA size greater than 5.5 cm can be prophylactically anticoagulated.
The data on left atrial size predisposing LA thrombus formation is controversial.
Maden et al first proposed that increased left atrial size is associated with increased risk of systemic embolism, which was supported by Sommerville and Chambers, who reported a threefold increase in embolism in patients with mitral stenosis with enlarged left atrial appendage on chest X-ray compared with those who did not.
These observations were not supported by subsequent studies, including a multifactorial study by Peterson et al.

LEFT ATRIAL SPONTANEOUS ECHOCONTRAST (LASEC)

Spontaneous echo contrast (SEC) or “smoke” is characterised by discrete, dynamic, swirling smoke-like echoes, under conditions of low shear rate of flow, i.e. low velocity gradient between adjacent fluid layers.
SEC probably results from erythrocyte aggregation or rouleaux formation, while some propose a role for platelet aggregation.
Left atrial spontaneous echo contrast (LASEC), occurs in conditions that favour blood stasis, including mitral stenosis, atrial fibrillation and LA enlargement. 80% to l00% of patients with LA thrombi has LASEC.
Of clinical importance LASEC is an independent predictor of thromboembolic risk in patients with MV disease, and in non valvular AF. In addition severe “smoke” showed a stronger association with LA thrombus and embolism than mild “smoke”.
Analysis of SEC includes consideration of site, extent, intensity, and whether constant or intermittent.
Intensity of LA, SEC is usually divided into two grades;
Marked SEC, visible at usual operative gain control of the equipment throughout the LA, and **Mild SEC,** appearing only at a high gain setting, in some portions of LA.
Recently LASEC has been classified into four grades.
Though SEC is associated with increased thromboembolic risk, there is no consensus in the literature, on what therapy is indicated in patients with LA “smoke.”
Patterns of blood flow in the left atrium are altered by mitral valve obstruction. Flow proximal to narrowed orifice accelerates as blood approaches the stenotic orifice, forming a high velocity jet in the orifice itself. Flow more distal to valve orifice also is altered.

ANALYSIS OF PULMONARY VENOUS DOPPLER FLOW IN MS BY TEE

Patterns of pulmonary venous Doppler flow are complex and is best visualised by TEE. As of now the pulmonary venous flow by Doppler echo, is not significantly variable between the different pulmonary veins.

Normally the pulmonary venous flow is pulsatile with forward flow in ventricular systole and diastole, followed by a backward or reversed flow during atrial systole. Forward triphasic flow pattern occurs often during normal heart rate ,with two peaks in ventricular systole viz, an early systolic , short low velocity jet (SI) (21+/- 17 cm/s) and a late systolic longer higher velocityjet (S 2) (55+/- 17 cm/s).
Forward biphasic flow pattern, occurs especially during sinus tachycardia, with one peak during systole (S) and other in diastole (D)
Normal pattern of pulmonary venous forward flow , manifests peak systolic flow greater than or equal to peak diastolic flow (S > D), with peak systolic to diastolic flow velocity ratio > 1). Backward flow is characterised by reversal of flow during atrial systole, producing a transient, small low velocity jet (A) (17+_5 cm/s).
Pulmonary venous Doppler flow pattern is altered by MS, but conflicting data have been reported in this regard
Keran et al in 1990 analysed pulmonary venous flow in MS by TTE.
In mild to moderate MS, the systolic (S) wave was more prominent. The diastolic (D) wave was continuous throughout to end of diastole, with a low flow shape and reduced peak velocity. In moderate MS, marked retrograde flow into the pulmonary veins (A wave) during atrial systole was observed. In severe MS. Pulmonary vein flow is decreased during systole, (S< D) and atrial flow reversal (A) is increased, with the magnitude of these changes corresponding to the degree of elevation of left atrial pressure.
Even in sinus rhythm, the increased volume of the left atrium leads to low velocity flow patterns, which predispose to development of atrial thrombi, particularly in the left atrial appendage.
Although the risk of left atrial thrombus formation and embolic events is thought to be low in MS patients in sinus rhythm, high prevalence of spontaneous contrast observed in TEE (upto 45% of patients)in this group raises the possibility of a higher embolic risk, even in sinus rhythm, in the presence of mitral stenosis.
Some patients in sinus rhythm have demonstrable thrombus, and in some patients with new-onset atrial fibrillation have LA thrombus suggesting thrombus formation before onset of AF.
The possible mechanism of atrial thrombus formation in sinus rhythm is the loss of atrial appendage mechanical function despite electrical evidence of sinus rhythm, leading to blood flow stasis.

ASSESSMENT OF LEFT ATRIAL APPENDAGE (LAA) FUNCTION

Left atrial appendage is a narrow finger like space, which is elongated and having narrow base located at posterolateral aspect of heart. Its size and function varies in different individuals. In patients with severe rheumatic MS left atrial appendage enlarges in size along with LA enlargement.
LAA function also altered in rheumatic MS, both in sinus rhythm and in atrial fibrillation. LAA function is commonly assessed by Doppler and 2D methods.
By two dimensional multiplane transesophageal echocardiography maximal and minimal LA appendage area were measured by planimetry and LAA ejection fraction calculated using formula;
LAA EF (%) = (LAA. max - LAA .min) / LAA. max X 100
LAA. Max-Maximal LAA area (end atrial diastole), LAA. Min - Minimum area (end atrial systole)-measured by planimetry.
Left atrial appendage function is assessed using pulsed Doppler imaging, with sample volume positoned at mouth of the appendage,the maximal velocity during atrial contraction is measured. This velocity corresponds to the force of atrial appendage contraction or emptying.
In normal individuals, left atrial appendage emptying velocity is greater than 50 cm/sec. Low left atrial appendage emptying velocity (<20 cm/sec) has been reported to significantly increase the embolic risk. Significantly lower velocities occur in patients with atrial fibrillation, and this finding has been associated with a predisposition for the development of left atrial appendage thrombus and the risk of thromboembolism.

ECHOCARDIOGRAPHC IMAGING OF LA THROMBUS

Conventional transthoracic echocardiography (TTE) has a poor yield in the detection of LA appendage thrombi. The sensitivity of TTE in detecting LA appendage clot is at the most 50%.

The posterior location of the LA in the chest as well as due to far field and side lobe artifacts as well as use of lower frequency transducers by TTE leads to the poor visualization of the LA appendage contribute to the lack of accuracy of TTE.

On the other hand, TEE is an excellent method for detecting atrial thrombi, especially those located in the LA appendage.

This is due to use of higher frequency transducers used in TEE as well as left atrium is a posterior structure lying in near field hence producing excellent image quality. Multiplane TEE allows imaging in numerous views thereby one can confidently diagnose or exclude LA and LA appendage thrombi. Infact TEE is 99% sensitive and 99 % specific in identifying left atrial thrombi.

Echocardiographically left atrial thrombus appear as amorphous, echogenic structure adherent to the endocardium whose appearance and texture are distinct from adjacent myocardium. They may be in variable shape and may be mobile and multiple.

An echo-lucent center may be present and it suggests that the thrombus is relatively new and actively growing.

Echocardiography can identify thrombi which are more likely to embolise. Risk factors include larger size, increased mobility, protrusion into the cavity of left atrium, heterogenous echo-density with echo-lucent center suggesting fresh thrombus.

Thrombus dimension $\geq$ 1.5 cm, history of thrombo embolism and mobile thrombus were considered as predictors of subsequent embolic events.

REVIEW OF LITERATURE

The predictors of thromboembolism in MS, is the present focus of interest. There is no correlation in MS, between the risk of embolism and NYHA functional cardiac status, MV area, MV calcification, and duration of AF.

The tendency for embolization in MS correlates directly with the age of the patient, size of the LAA, and indirectly with the cardiac output.MS patients more than 35 years of age, with dialation of LAA, and with low cardiac output are at the highest risk of emboli. In a recent retrospective generalized study with TEE, it was observed that MS, LA dilatation and severe left ventricular dysfunction are independent risk factors for LAA thrombus formation. In addition, atrial fibrillation and left atrial spontaneous echo contrast have been associated with increased risk of cardiogenic embolism in MS

Gaswami et al prospectively investigated various clinical and echocardiographic variables to predict the left atrial and left atrial appendage clot and spontaneous echo contrast in patients with severe rheumatic mitral stenosis. They studied 200 consecutive patients (112 males and 88 females; mean age 29.6+1-9.6 years). Left atrial clot and spontaneous echo contrast were present in 26 and 53.5% of cases, respectively. There were no significant differences in the mitral valve area, mean transmitral diastolic gradient and left ventricular ejection fraction between patients with and without clot.

Gonzalez-Torrecilla et al investigated the independent factors associated with the presence of left atrial (LA) spontaneous echo contrast (SEC) and thromboembolic events in patients with mitral stenosis (MS) in chronic atrial fibnllation (AF) Transesophageal and transthoracic echo studies were performed in 129 patients with MS in chronic AF. Previous embolic events were documented in 45 patients, 20 of them within 6 months, and 65 patients were receiving long-term anticoagulation.

The intensity of LASEC and mitral regurgitation, the presence of thrombi and active LA appendage flow (peak velocities > or = 20 cm/s), and LA volume as well as other conventional echo-Doppler determinations were investigated in every patient. The prevalence of significant LASEC (degrees 3+ and 4+), thrombus, active LA appendage flow, and significant mitral regurgitation (>2+) were: 52% (67 patients), 29.5°A, (38 patients), 32% (41 patients), and 36% (47 patients), respectively. Multivariate analysis showed that decreasing mitral regurgitation severity, absence of active LA appendage flow, and mitral valve area were the independent correlates of LASEC (odds ratio -3.7, 5.4, and 0.17, respectively; all $p < 0.02$). Active LA appendage flow and anticoagulant therapy were associated negatively, whereas the severity of LASEC was associated positively with the finding of LA thrombus (OR 9.6, 3.9, and 1.6, respectively; all $p < 0.05$). The intensity of LASEC and previous anticoagulant therapy (OR 1.74 and 4.5, respectively, $p < 0.005$) were the independent covariates of thrombi and/or recent embolic events.

Patients with clot were older (34.4+1-11.4 vs. 28.2+1-8.5 years, P<0,001), had longer duration of symptoms (41. 4+/-36.0 vs. 28.8+1-22.9 months, P<0.001), more frequent atrial fibrillation and spontaneous echo contrast (69.2 vs. 16.9%, P<0. 00001 and 76.9 vs. 45.3%, P<0.00001, respectively) and larger left atrial area and diameter (41.0+1-12.7. vs. 29.9+/-7.4 cm(2), P<0.00001 and 53.9+/-8.3 vs. 47.6+/-7.4 mm, P<0.0001, respectively) as compared to patients without clot. Similarly patients with spontaneous echo contrast were older (3 1+/-10,4 vs. 27.8+/-8.3 years, P<0.01), had more frequent atrial fibrillation (48.6 vs. 9.7%, P<0.0001), left atrial clot (37.4 vs. 12.9%, P<0.0001), larger left atrial area and diameter (37.6+/-11.2 vs. 28.1+/-6.7 cm(2), P<0.00001 and 52,2+1-8.3 vs. 45,9+/-6.5 mm, P<0.00001, respectively) and smaller mitral valve area (0.77+/-0.14 vs. 0.84+/-0.13 cm(2), P'<0.01) as compared to patients without spontaneous echo contrast.

There were no significant differences in the mean transmitral diastolic gradient and left ventricular ejection fraction. On multiple regression and discriminant function analysis, atrial fibrillation and left atrial area were independent predictors of left atrial clot formation. In a subgroup of patients with sinus rhythm, larger left atrial area and presence of spontaneous echo contrast were significantly associated with the presence of clot in left atrium and appendage.

They concluded that in patients with severe mitral stenosis, the presence of atrial fibrillation and in the subgroup of the patients with sinus rhythm the presence of large left atrium and spontaneous echo contrast were associated with higher risk of clot formation in the left atrium and might be benefited by prophylactic anticoagulation.

In conclusion, the severity of mitral regurgitation and lack of active LA appendage flow were, respectively, the strongest independent correlates of significant LASEC and thrombus in patients with MS in chronic AF. LASEC remains the cardiac factor most strongly associated with thrombus and/or recent embolic events in these patients.

Acarturk E et al studied the thromboembolism risk in patients with mitral stenosis. They evaluated a total of 168 consecutive patients with predominant rheumatic mitral stenosis by transthoracic (TTE) and trarisesophageal echocardiography (TEE). Of the 168 patients, 35 had previous embolic events (group I) and 133 had no emboli (group 11). A total of 77 (45.8%) patients had atrial fibrillation. The frequency of atrial fibrillation was higher in group I than group II (68.6% vs 39.8%, $p < 0.001$). The incidence of left atrial enlargement was greater in group I ($p < 0.001$). Mitral valve area was found to be smaller in group I compared to group II ($p < 0.001$). In group 1 83.3% and 29.2% of the patients with atrial fibrillation had left atrial spontaneous echo contrast (SEC) and left atrial thrombus, respectively, and 72.7% of the patients with sinus rhythm had left atrial SEC. In group II 79.2% and 20.8% of the patients with atrial fibrillation had left atrial SEC and left atrial thrombus whereas 28.6% and 2.6% of the patients with sinus rhythm had left atrial SEC and left atrial thrombus, respectively.

The incidence of left atrial thrombus was significantly different in those patients with compared to those without embolic events (20% vs 9.7%, $p < 0.01$).

In groups land II, 28 of35 (80%) and 64 of 133 (48.1%) patients had left atrial SEC ($p < 0.01$). Patients with left atrial SEC had a greater left atrial size ($p < 0.01$) and smaller mitral valve area ($p < 0.01$). Left atrial size was normal in 2 patients with left atrial SEC and SEC was not found in 55 patients with enlarged left atrium. Multiple logistic regression analysis showed that atrial fibrillation, mitral valve area and left atrial enlargement were independent predictors of the SEC ($p < 0.001$) and left atrial SEC was the principal determinant of thromboembolism.

They concluded that that regardless of rhythm and atrial size, left atrial SEC is principal determinant of thromboembolic risk in mitral stenosis and suggested that TEE may be able to detect those patients with mitral stenosis at risk for emboli and guide appropriate therapy.

S J Saidi et al studied the incidence and factors influencing left atrial clot in patients with mitral stenosis and normal sinus rhythm. In their study, no meaningful relation was found between left atrial size and the presence of a clot in the left atrium, or between age and clot formation. On the other hand, despite the fact that the mean mitral valve score in the MS group in NSR with a clot was higher than the group without a clot, the difference was not significant. Another result of this study was the comparison of clot frequency in patients in NSR with those in AF rhythm. Clotting was more common in the AF group, with the difference being significant, as could be expected. Age of the patients in AF rhythm in that study was significantly higher than the group in NSR.

Concerning the left atrial size, mitral valve score and valve gradient, obtained values were significantly higher in the AF group compared to the group in NSR. Also concerning the coexistence of MR with MS and its effect on inhibiting clot formation, their study showed a lower percentage of clotting in the combined pathology (MS and MR) group compared to the pure MS group, although the difference was not significant. This could be because the MR present in the majority of the patients in this study was of mild severity.They concluded that despite the fact that left atrial clot is usually sought in MS patients with AF rhythm; MS patients in NSR are also at risk from intra-atrial clot formation. Although this risk is less than the AF rhythm group, it is sufficient to warrant measures for prevention of thromboembolic episodes in this group of patients.

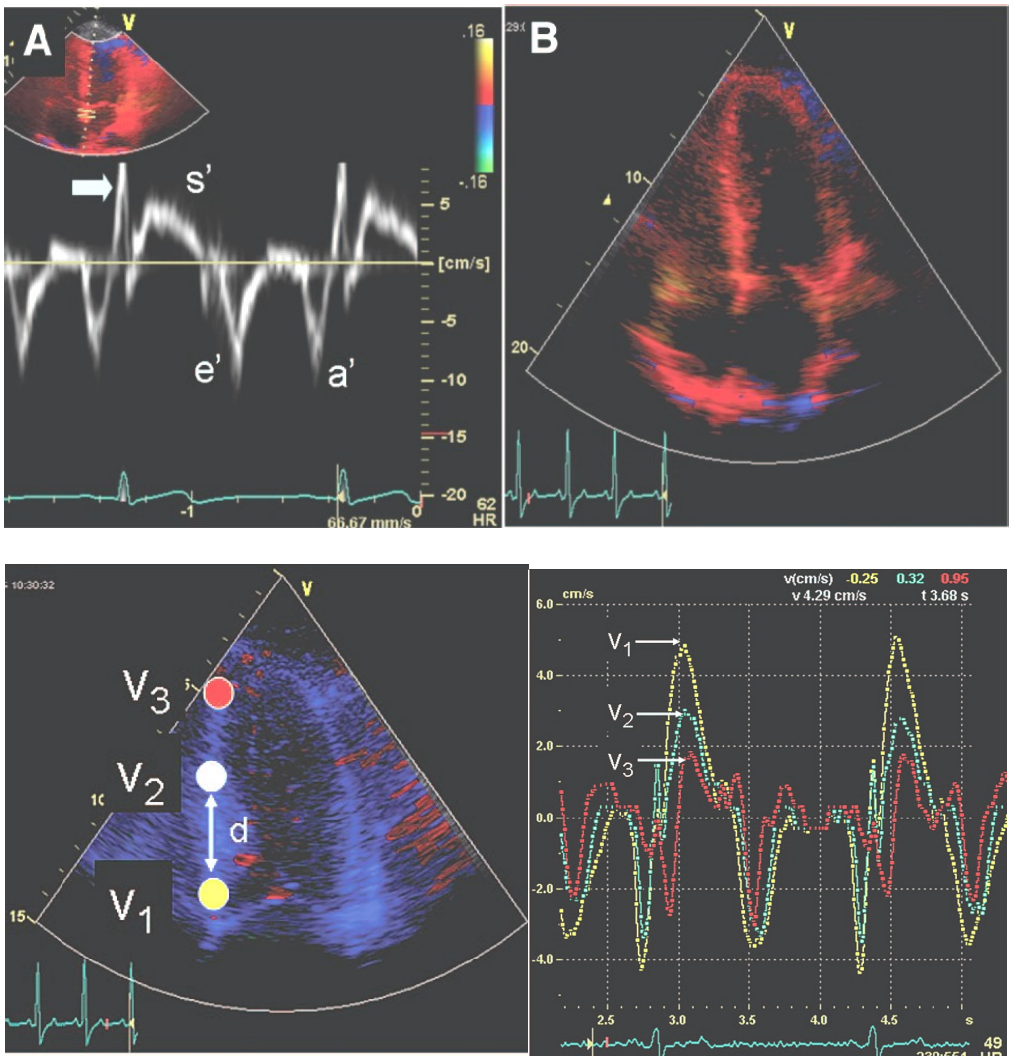
Leting et al performed transesophageal echocardiograms in 289 patients over a 6 year period. They found 94 patients (3.2 %) to have left atrial thrombus. The thrombi were considered as mobile in 45

patients .Seventeen patients had suffered from a stroke or embolic event (event rate: 10.4% per year) and 27 had died (mortality: 15.8% per year) during a follow-up period of 19.2 months.
Thirty-three patients had thrombus with a maximum dimension 1.5 cm. Thrombus dimension ≥ 1.5 cm, history of thrombo-embolism and mobile thrombus were considered as predictors of subsequent embolic events.
Doppler tissue imaging uses the same principles as colour flow Doppler mapping, applying standard autocorrelation processing but reversing high velocity and low amplitude filters such that the high amplitude/low velocity motion of tissue is displayed in preference to blood flow.As cardiac structures move in a velocity range 0.06 to 0.24 m/s, some 10 times slower than myocardial blood flow, and have an amplitude approximately 40 decibels higher, it is possible to obtain images of tissue Doppler motion of high resolution without significant artifact originating from the blood pool. In such images, each pixel displays one colour representing a mean velocity value. However, comparison with pulsed wave Doppler traces of myocardial motion has indicated that initial Doppler tissue images failed to accurately quantify accurately each phase of the cardiac cycle. The normal cardiac cycle has four distinct peaks in systole and diastole

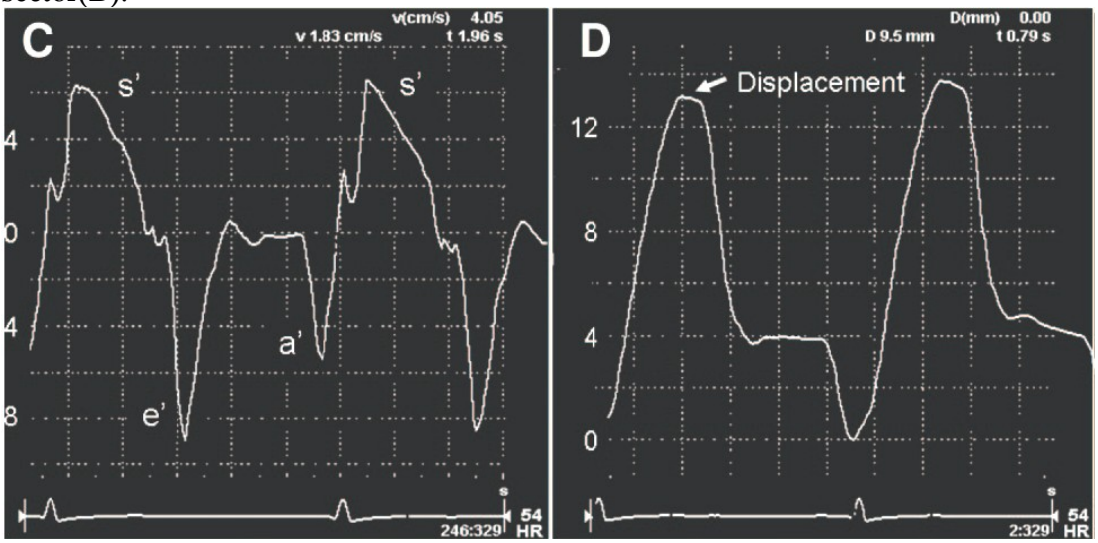
Visual or semiautomated tracking of the endocardial border provide estimates of cardiac Volume, which are used to derive ejection fraction, a quantitative indicator of ventricular function. However, the heart is a complex mechanical organ that undergoes cyclic changes in multiple dimensions that ultimately effect a change in chamber volume that results in ejection of blood. Regardless of imaging technique, ejection fraction is unable to provide information on the underlying myocardial mechanical activity. Also, ejection fraction reflects the sum contribution of several regions and does not provide information on regional function. Regional function assessed visually is subjective and prone to error.

Quantification of regional myocardial activity was feasible only in experimental studies by use of markers attached directly to the myocardium, a technique not practicable in the clinical realm. Myocardial tagging with cardiac magnetic resonance (CMR) introduced the opportunity to noninvasively track regional myocardial mechanics. Modifications to the filter settings on pulsed Doppler to image low-velocity, high-intensity myocardial signal rather than the high-velocity, low-intensity signal from blood flow allows similar assessment by ultrasound. This technique is commonly referred to as tissue Doppler imaging (TDI) or Doppler myocardial imaging.

The TDI method depicts myocardial motion (measured as tissue velocity) at specific locations in the heart. Tissue velocity indicates the rate at which a particular point in the myocardium moves toward or away from the transducer. Integration of velocity over time yields displacement or the absolute distance moved by that point



Tissue velocity tracing tracks myocardial motion at the point of interrogation. Pulsed Doppler (A) yields myocardial motion only at the region of interest. In this example, the sample volume is located in the basal septum off an apical 4-chamber view. Color TDI collects tissue velocity from the entire sector(B).

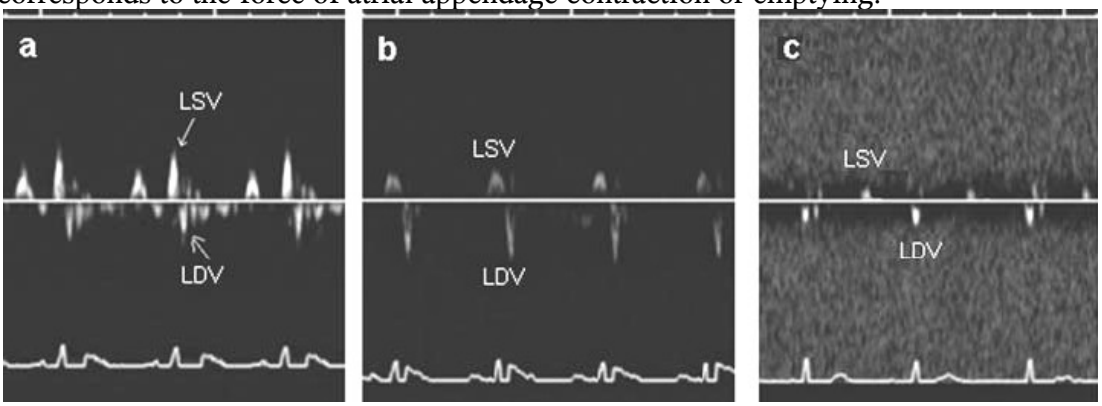


With color TDI, the region of interest can be placed anywhere in the sector to yield tissue velocities

(C). In the longitudinal orientation (apical views), the base moves toward the apex in systole and depicts a positive polarity (s_) and moves away from the apex to yield the early (e_) and late (a_) negative diastolic velocities. Integration of the tissue velocity signal yields displacement (D) that indicates the distance moved by that point.

Tissue velocity tracing tracks myocardial motion at the point of interrogation. Pulsed Doppler yields myocardial motion only at the region of interest. With color TDI, the region of interest can be placed anywhere in the sector to yield tissue velocities. In the longitudinal orientation (apical views), the base moves toward the apex in systole and depicts a positive polarity (s') and moves away from the apex to yield the early (e') and late (a') negative diastolic velocities.

Tissue Doppler–derived velocity can be obtained via pulsed Doppler (by placing a sample volume at a particular location), M-mode Doppler, or 2-dimensional color Doppler. Color Doppler acquires tissue velocity information from the entire sector, and thus, multiple sites can be interrogated simultaneously. Individual segments are analyzed *ex post facto*. Although all of these methods yield the same mechanical information, differences in the peak values exist. Pulsed Doppler measures peak velocity, which is ≈20% to 30% higher than the mean velocity measured by color Doppler. This difference should be considered when one estimates left ventricular filling pressure using the E/e' ratio. Frame rates are highest with the M mode, lower with pulsed Doppler, and lowest with color Doppler TDI. Tissue Doppler has been validated extensively and examined in a variety of cardiac pathologies. Although initial work reported tissue velocity from the septal or posterior wall in the parasternal projections, recent work almost exclusively interrogates tissue velocities in the longitudinal direction (apical projections). In the longitudinal direction, myocardial motion is such that the apex is generally immobile, whereas the base moves toward the apex in systole and away from the apex in diastole. This differential motion between base and apex results in a velocity gradient along the myocardial wall, with the highest velocities at the base and low or zero velocity at the apex. Because TDI interrogates motion at a single point in the myocardium with reference to a point outside the chest (the transducer), it is influenced by translational motion and tethering (normal apical segments pull an abnormal basal segment toward the apex). Moreover, single-point interrogation (depicting tissue displacement) does not fully capture true myocardial mechanics.
In the longitudinal orientation, normal heart motion is such that the base moves toward the apex, which moves little or not at all. Thus, tissue velocity is maximum at the base (V1), lower in the mid heart (V2) and least at the apex (V3). This gradient in velocities is used to calculate strain rates. Strain rate is calculated with tissue Doppler as the difference between 2 tissue velocities along the ultrasound beam (V2_V1).
Left atrial appendage function is assessed using pulsed Doppler imaging, with sample volume positioned at mouth of the appendage; the maximal velocity during atrial contraction is measured. This velocity corresponds to the force of atrial appendage contraction or emptying.



LAA tissue Doppler recordings were performed by the sample volume of PWD placed on LAA lateral wall .In cases with quadriphasic wave pattern , LAA late peak systolic wave (LSV ,the positive wave observed after the P wave) and late peak diastolic wave (LDV , the negative wave following LSV) velocities were recorded .In patients with sinus rhythm and biphasic wave pattern or atrial fibrillation (AF) , positive and negative wave velocities were accepted as LSV and LDV, respectively

MATERIAL AND METHODS

This study was performed in the Department of Cardiology, Government General Hospital, Chennai, during the year 2006–2009. The study is a prospective case control study involving 48 patients.

STUDY GROUP SELECTION:

Ethical committee clearance was obtained to conduct the study in our hospital.
All subjects provided written informed consent to participate in the study before inclusion.

Inclusion Criteria:

1. Patients with isolated mitral stenosis
2. No significant other (more than mild) valve lesion.(except tricuspid regurgitation secondary to pulmonary hypertension)
3. NYHA Class I-III status

Exclusion Criteria:

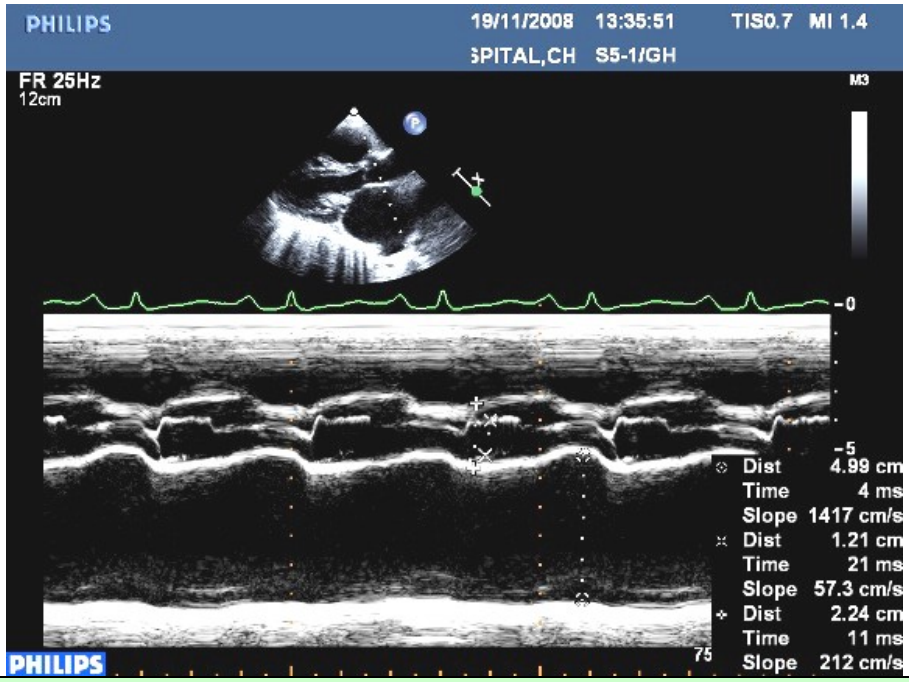
1. Patients with NYHA Class IV status
2. Significant other (more than mild) valve lesion
3. Significant co-morbid conditions.
4. Previous cardiac surgery including closed mitral commissurotomy
5. Pregnancy and puerparium
6. Patients with hypertension, diabetesmellitus, evidence of coronary artery disease.

The controls were with age and sex matched who underwent TEE due to suspicion of various cardiac diseases and had normal TEE examination

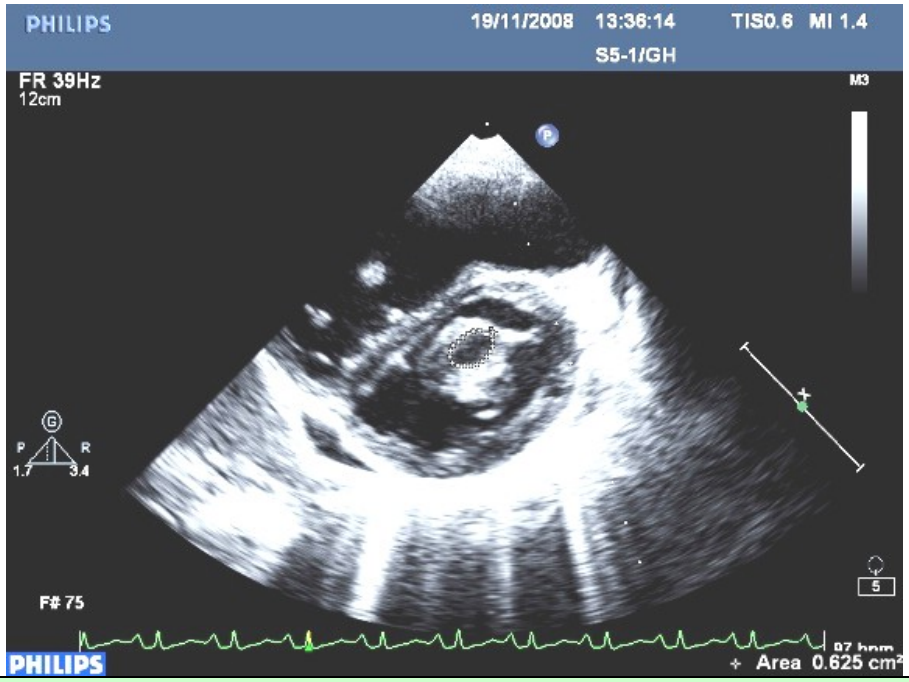
1. Patient characteristics:

The study population included 48 patients (35 male and 13 female) who attended the outpatient department Govt. General Hospital, Chennai-3, the patients were divided into two groups:
Group 1 – Patients with sinus rhythm and LAAEV >25 cm/sec (n = 20)
Group 2 – Patients with sinus rhythm and LAAEV <25 cm/sec (n = 16)
Group 3–Patients with atrial fibrillation (n=9)
A complete Transthoracic echocardiogram was obtained including
M- mode, 2D, colour Doppler and pulse& continuous wave Doppler in every patient. PHILIPS ie33 echo machine is used for this study. A 2.5 MHZ probe is used for transthoracic echocardiography and a 5 MHZ multiplane probe is used for transesophageal echocardiography.
Lesion severity in individual valve was characterised by various methods.
Specific attentions were paid in assessing mitral valve morphology, Wilkinson's scoring, and mitral valve area by planimetry & pressure half time method, peak and mean transmitral gradient.
Left ventricular ejection fraction (EF) was calculated by using modified Simpson's technique. M-mode echocardiograms at mitral & aortic valve level were obtained routinely for measurement.
Left atrial dimensions were measured in end systole in PLAX- antero posterior and two orthogonal diameters in four chamber view and left atrial volume calculated by using prolate ellipse method.
Left atrial volume = (Dl X D2 X D3) X 0.523
Left atrial appendage was visualised in PSAX view at aortic valve level and LAA thrombus is characterized by measuring its major and minor dimensions. A focused transoesophageal echocardiogram was obtained for all patients.
Transesophageal echocardiography is a very accurate technique to interrogate the left atrium for thrombi. Multiple views are used to visualise the entire left atrium for identifying evidence of thrombi. Specific attention was given to left atrial appendage from variety of planes, the appendage can be easily

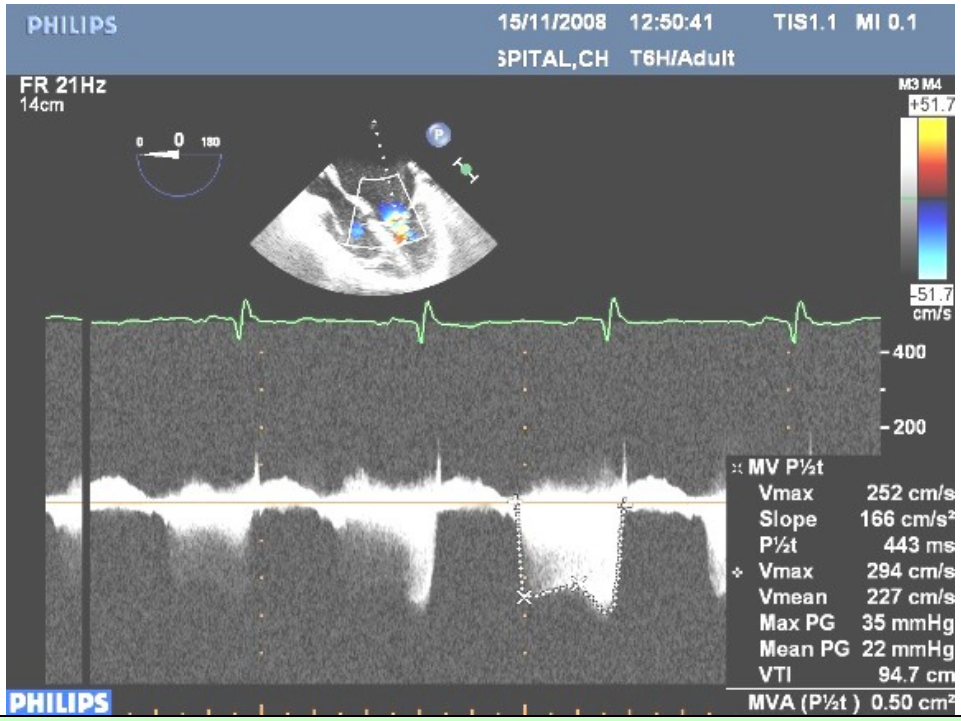
visualised. It lies just below the left upper pulmonary vein and is separated from the vein by a ridge of tissue.
Care was taken to distinguish normal trabeculation from localised thrombus formation.Trabeculae tend to be more linear and are continuous with the atrial wall in more than one view.Thrombi typically protrude into the appendage, often with independent motion.
Once visualised thrombi is assessed for size, mobility and whether it extends to body of the left atrium. Size of the thrombus is measured as major and minor dimensions.
LA appendage area in diastole & systole were measured and LAA ejection fraction calculated using formula;
LAA EF (%) = (LAA.max -LAA .min)/LAA. max X 100
LAA.max-Maximal LAA area (end atrial diastole), LAA.Min.- Minimum area (end atrial systole)- by planimetry.
Left atrial appendage function is assessed using pulsed Doppler imaging, with sample volume positioned at mouth of the appendage; the maximal velocity during atrial contraction is measured. This velocity corresponds to the force of atrial appendage contraction or emptying.
Pulmonary venous pulsed wave Doppler was obtained from left upper lobe pulmonary vein. Entire left atrium was searched for thrombus and specific note was made on mitral valve morphology and left atrial spontaneous echo contrast.
Transesophageal echocardiography. Multiplane TEE was performed in all subjects. The presence of SEC and thrombi were examined with appropriate gain setting to avoid noise artifacts. SEC was diagnosed by the presence of dynamic smoke like echoes in the left atria (LA) cavity and LA appendage with a characteristic swirling motion . The severity of SEC was graded from 0 to 4+.
The LAA flow profiles were obtained by placing the sample volume of the PWD into the orifices of the appendage. LAAEV and filling (LAAFV) velocities were recorded. LAAEV and LAAFV were averaged for six consecutive cardiac cycles.
LAA tissue Doppler recordings were performed by the sample volume of PWD placed on LAA lateral wall .In cases with quadriphasic wave pattern, LAA late peak systolic wave (LSV,the positive wave observed after the P wave) and late peak diastolic wave (LDV , the negative wave following LSV) velocities were recorded .In patients with sinus rhythm and biphasic wave pattern or atrial fibrillation (AF) , positive and negative wave velocities were accepted as LSV and LDV, respectively. LSV and LDV were averaged for six consecutive cardiac cycles.
All patients received standard medical treatment with, Digoxin, Penicillin, KCL syrup, Verapamil, Dieuretics and other drugs as clinical condition warrants.



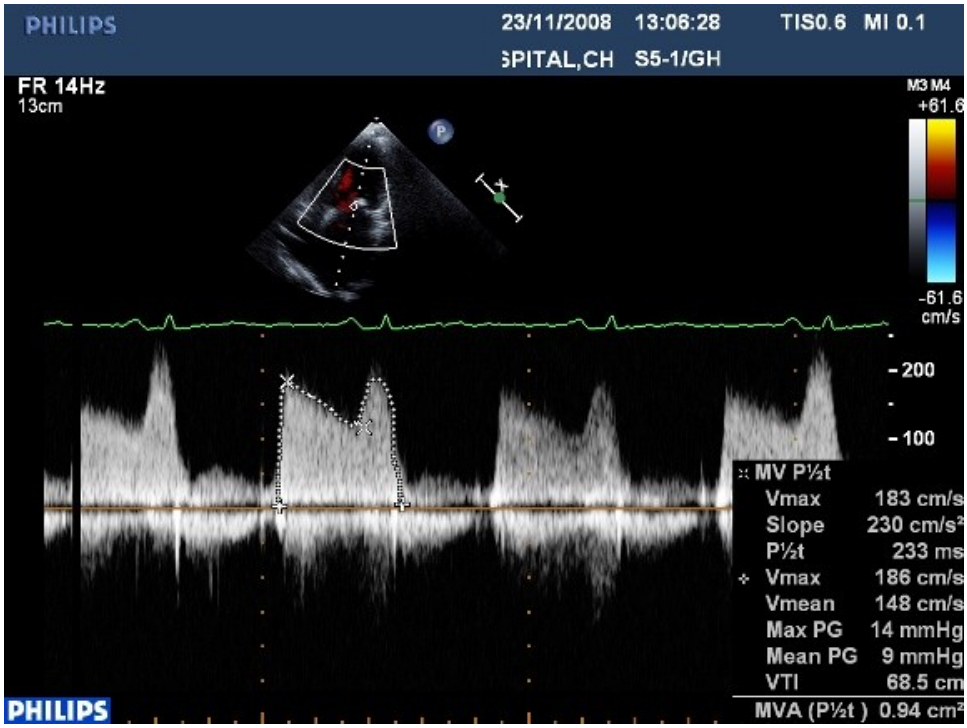
Picture-1 M-mode Echo of Parasternal long axis view showing measurement of LA diameter



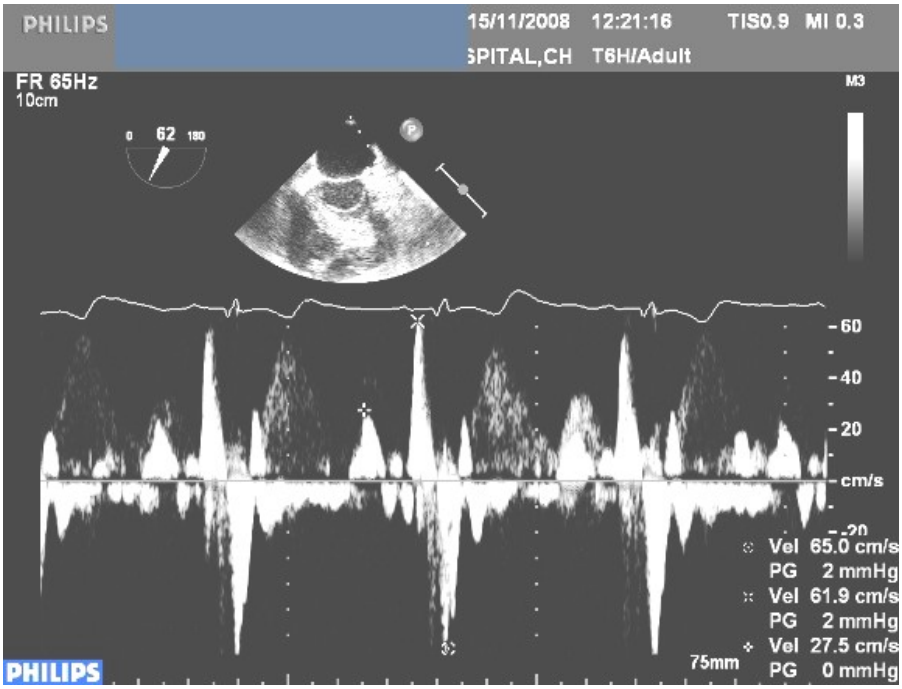
Picture-2 2D-Echo Parasternal short axis view showing measurement of Mitral valve annulus.



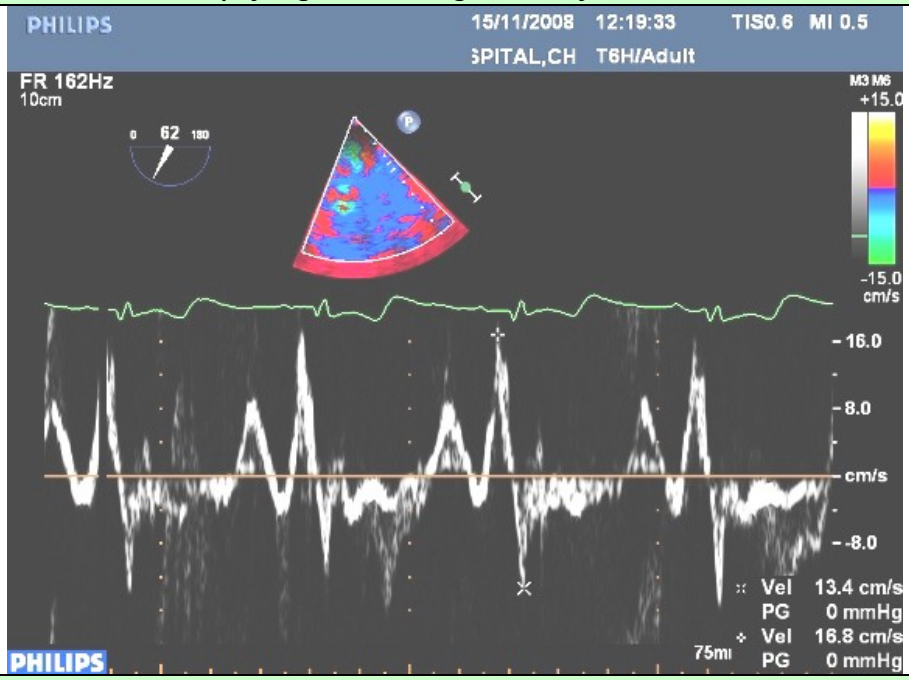
Picture-3 TEE 2D Echo continuous wave Doppler flow across mitral valve showing mitral valve gradient.



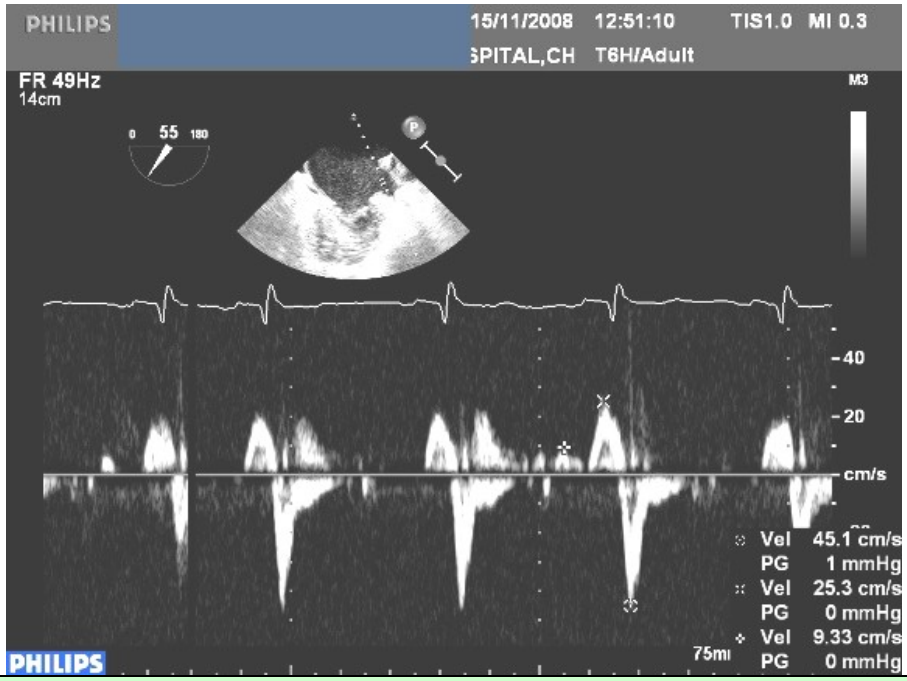
Picture-4 – TTE 2D echo continuous wave Doppler across mitral valve showing MV gradient.



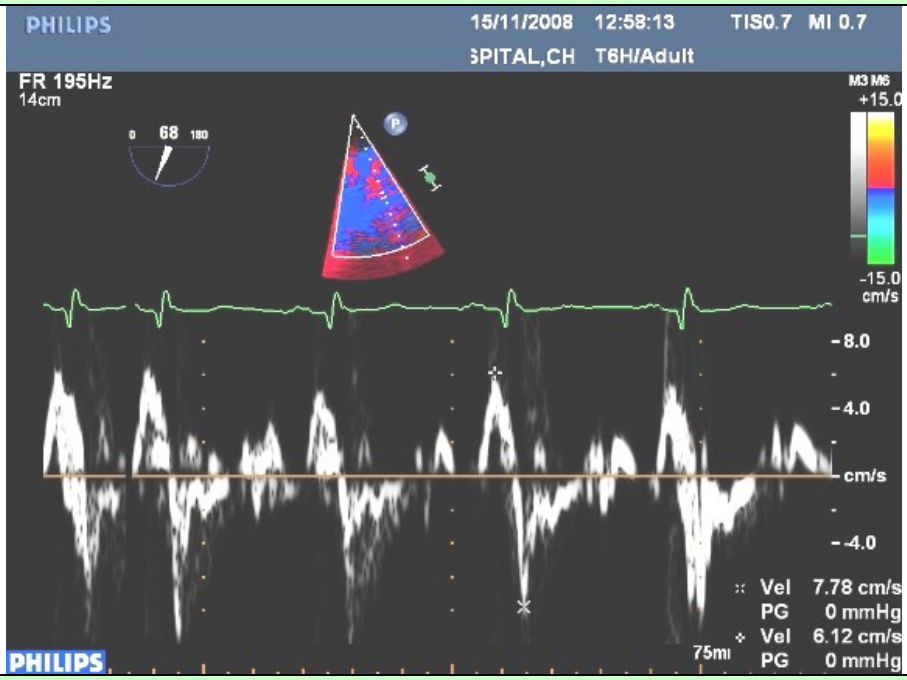
Picture 5 – TEE showing Pulse Doppler imaging across LAA showing normal emptying and filling velocity.



Picture 6 – Tissue Doppler imaging across LAA lateral wall, showing reduced LSV & LDV.

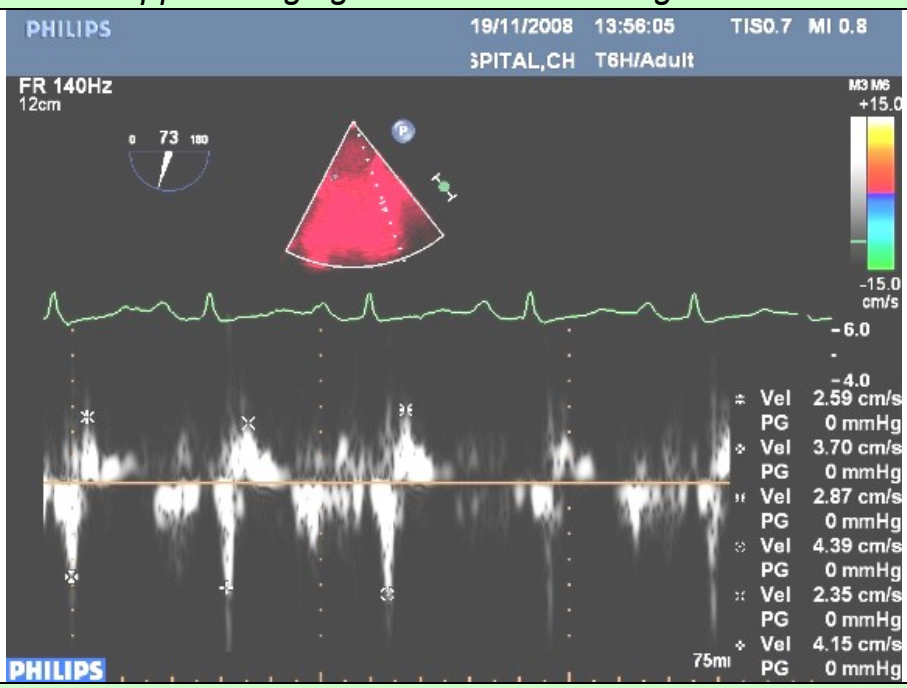


Picture-7 – Pulse Doppler imaging across LAA. In a patient with AF showing reduced LAAEV & LAAFV

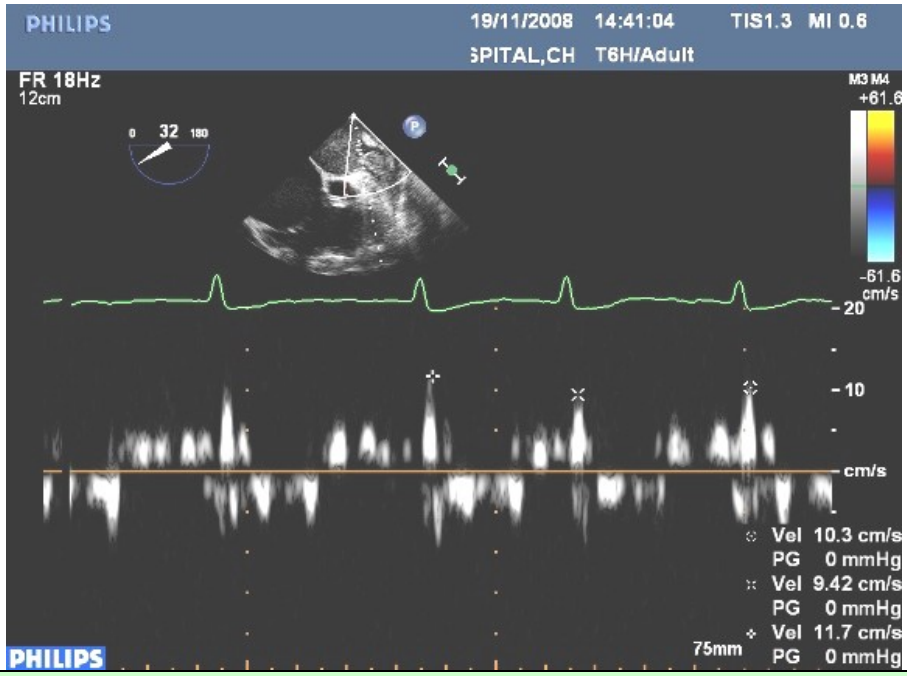


Picture-8 – Tissue Doppler imaging across LAA lateral wall in a patient with AF

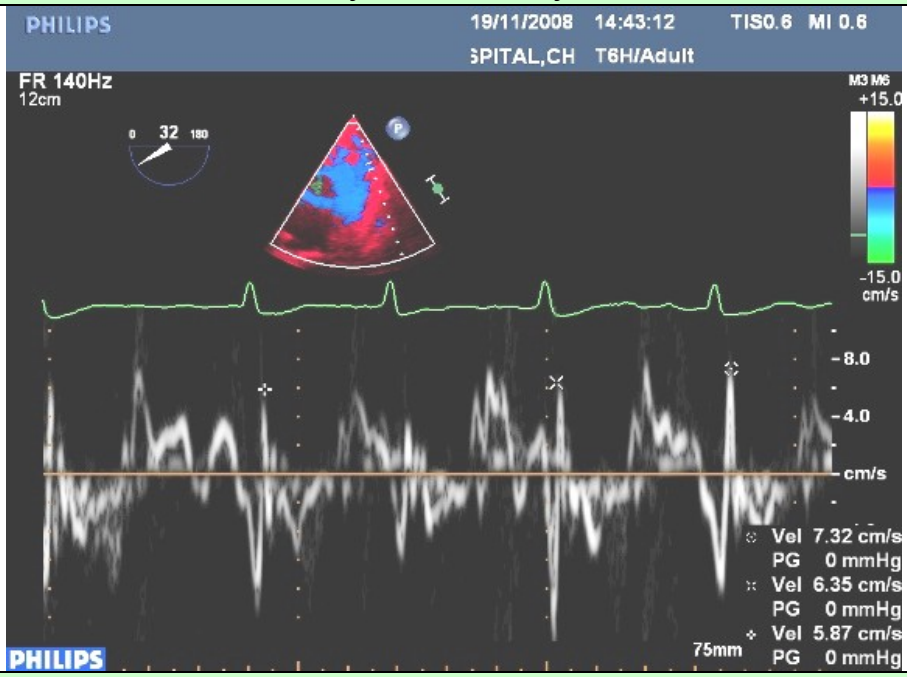
Picture-9 – Pulse Doppler imaging across LAA showing reduced LAAEV & LAAFV



Picture-10 – Tissue Doppler imaging across LAA. Lateral wall showing reduced emptying and filling velocity.



Picture-11 – Pulse Doppler imaging in a patient with LAA thrombus showing reduced systolic velocity



Picture-12 – Tissue Doppler – imaging in a patient with LAA thrombus showing reduced emptying velocity

STATISTICAL ANALYSIS

All calculations were performed with Statistical Package for the Social Sciences 10. Continuous variables were expressed as mean value +/- SD and compaired with the unpaired Student‘s t – test. Categorical variables were tested with the chi – square test. Person correlation analysis was used to establish the association between SEC density and LAAEV and LSV. A receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cutoff point of LAAEV and LSV to discriminate between patients with and without thromboembolic events. The area under the curve value was calculated. Multivariate logistic regression analysis was used to identify the independent determinants of thromboembolic events. Age ,rhythm , EF , LA dimension , MVA , SEC , thrombus , LAAEV , LAAFV , LSV ,and LDV were selected in the multivariate model.

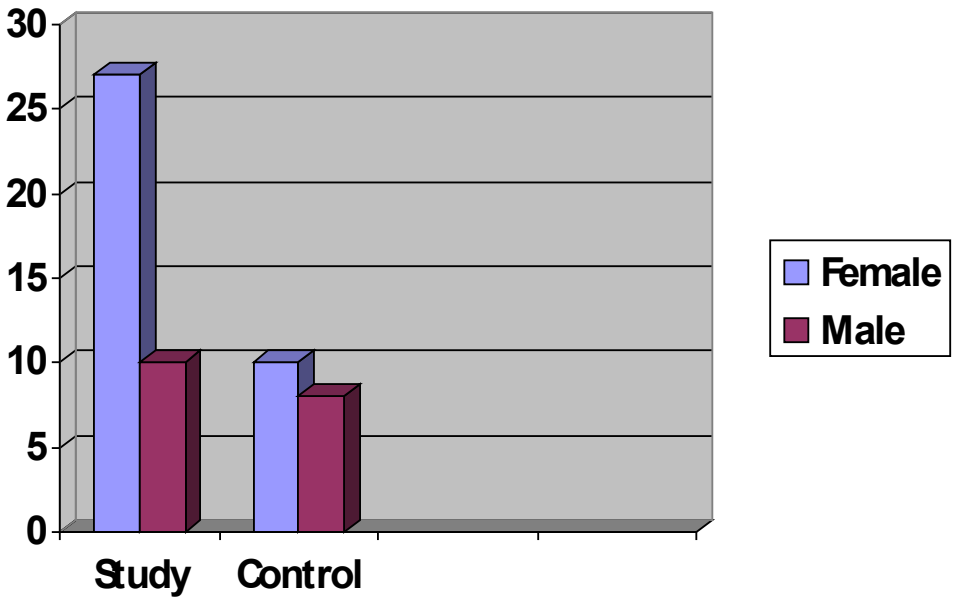
RESULTS

Clinical and Echocardiographic Characteristics of the Patients and the Controls.

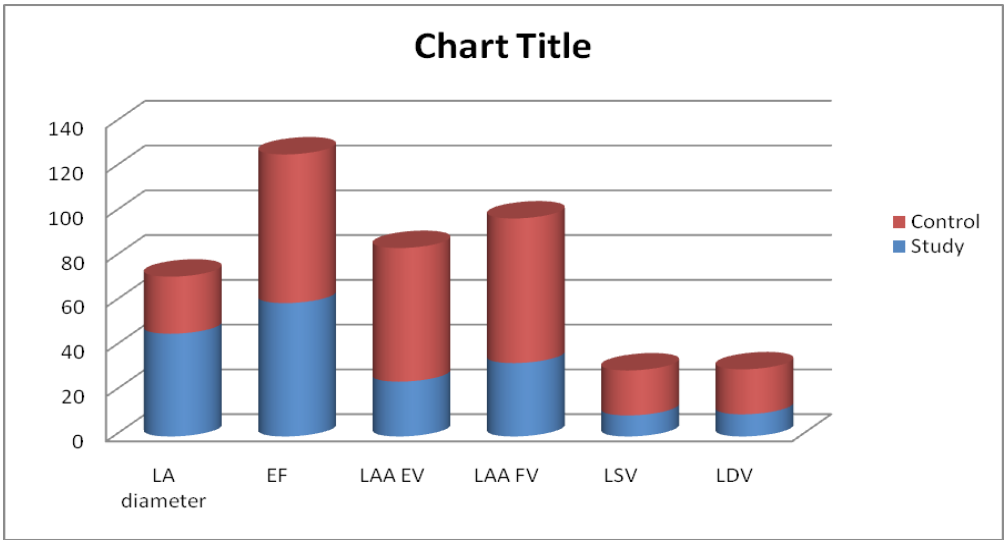
Table I shows the Clinical and Echocardiographic Characteristics of the Patients and the Controls

Table-I: Clinical and Echocardiographic Characteristics of the Patients and Controls

	Controls n=(18)	***Patients n=(48)***	***P***
Age(years)	35.1 ± 3.8	30.83 ± 3.8	
Gender(F/M)	10/8	27/13	
EF(%)	66.4 ± 2.1	59.6 ± 2.8	<0.001
LA diameter(mm)	25.1 ± 1.24	45.9 ± 3.0	<0.001
LAAEV(cm/sec)	59.7 ± 5.0	24.5 ± 5.1	<0.001
LAAFV(cm/sec)	64.6 ± 5.7	32.8 ± 5.0	<0.001
LSV (cm/sec)	20.1 ± 1.7	9.4 ± 1.9	<0.001
LDV(cm/sec)	20.1 ± 3.3	9.9 ± 1.8	<0.001
Thrombus	(0.0)	9(18.7)	<0.001
SEC	(0.0)	26(56.5)	<0.001



Echocardiographic Characteristics of the Patients and Controls



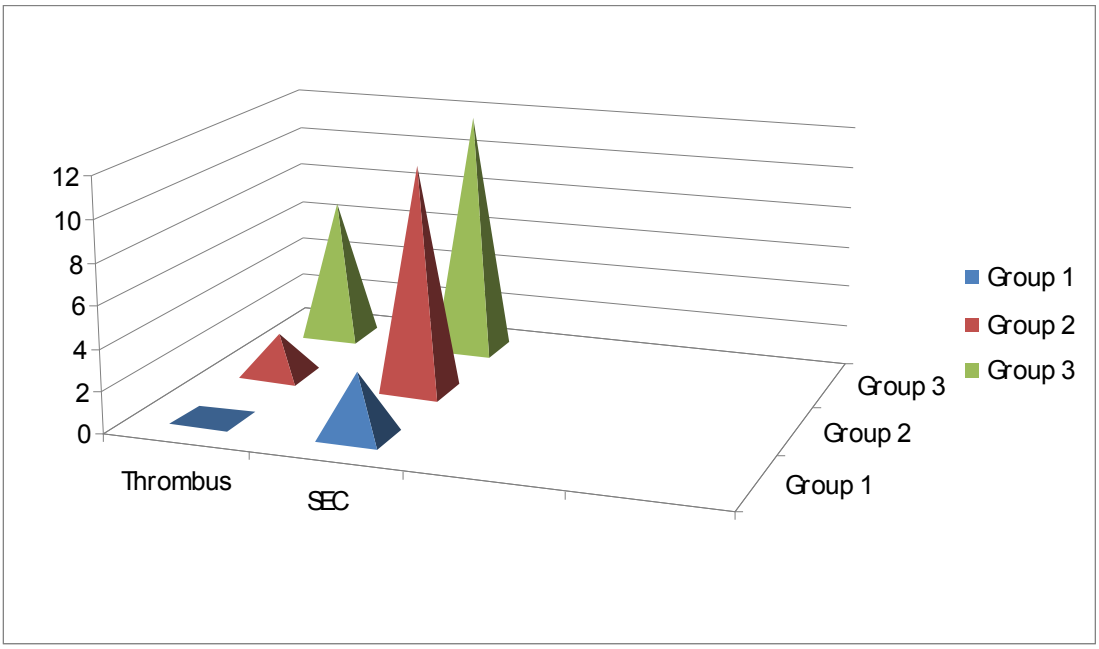
The mean MVA was 1.28 +/- 0.32 cm2 in patients. 12 patients had AF and 7 had thromboembolic events (stroke in6, one patient had TIA). Thromboembolic events had occured 5.0 +/- 4 months before TEE examination .The patients had larger LA size and lower LAAEV, LAAFV, LSV, and LDV than controls. However, age, gender, and EF were similar. Thrombus and SEC were detected in 9(18.7%) and 26 (56.5%) patients, respectively.

Table-2 Clinical and Echocardiographic Characteristics of the Patients and Groups

	Group I n=(20)	***Group II n=(16)***	***Group III n=(12)***	***P 1***	***P 2***	***P 3***
Age(years)	30.4±3.4	31± 3.2	29±2.5			
Gender(F/M)	14/6	12/4	9/3			
Thromboembolic events	0(0)	3(18)	4(33)		<0.001	
EF(%)					<0.001	0.5
LA diameter(mm)	58.7±2.4	59.6±3.3	60.2±2.6	0.006	<0.001	0.02
MVA(sq.cm)	43.5±2.2	46.2±3.1	45.4±2.4	0.009	<0.001	0.9
LAAEV(cm/sec)	1.4±0.4	1.2±0.32	0.8±0.27	<0.001	<0.001	0.2
LAAFV(cm/sec)	34.3±5.2	19.6±4.4	14.2±3.1	<0.001	<0.001	0.1
LSV (cm/sec)	39.5±4.2	23±3.6	19.4±3.3	<0.001	<0.001	0.03
LDV(cm/sec)	12.4±	9.0±1.7	5.8±1.9	<0.001	<0.001	<0.05
Thrombus	12±1.6	9.1±1.4	7.2±1.0	0.002	<0.001	

SEC	0(0.0) 3(29.0)	2(12) 11(68.7)	7(58) 12(100)		<0.001 <0.001	

Echocardiographic Characteristics of the PatientGroups

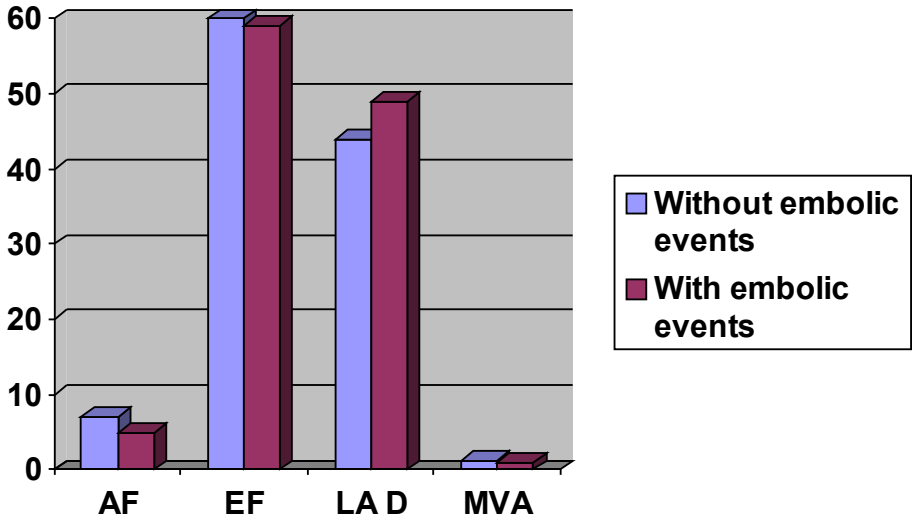


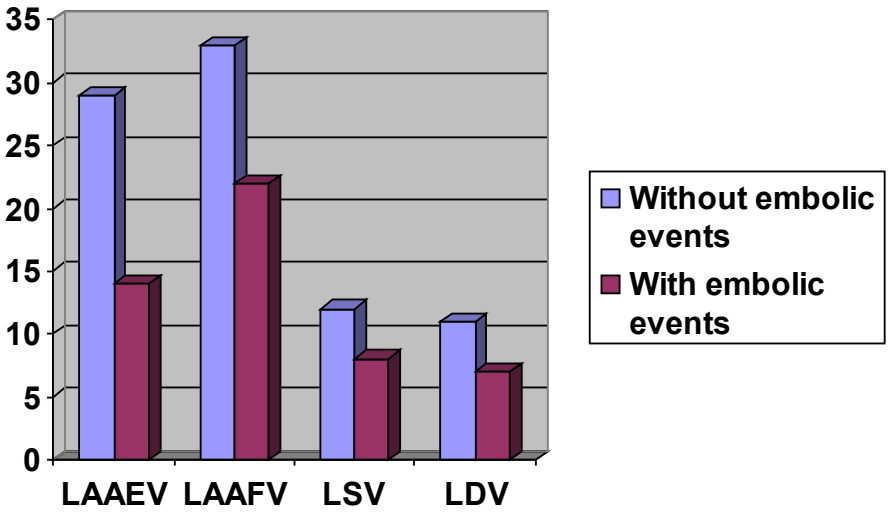
The Group I patients had a lower LA size, higher EF, larger MVA, and a higher LAAEV, LAAFV, LSV, and LDV. The Group III patients had higher thromboembolic events, larger LA size, lower LSV and LDV, and higher frequency of thrombus and SEC than the other groups. MVA, EF, LAAEV, and LAAFV were similar in Group II and III.

SEC was observed in 29% of Group I patients, whereas it was not detected in 31.3% of Group II patients. Both LAAEV and LSV were decreasing, while the SEC frequency and density were increasing from Group I to Group III. SEC was strongly correlated with LSV ($p<0.001$), whereas weakly correlated with LAAEV ($p=0.01$)

Table-3 Comparison of Patients with and without Thromboembolic Events

	With out Embolic Events. n=(41)	With Embolic Events. n=(7)	P
Age(years)	30.1 ± 3.3	29 ± 3.2	
AF	7(17)	5(71)	<0.001
EF (%)	60.5 ± 2.6	58.9 ± 2.4	0.02
LA diameter(mm)	44.2 ± 3.3	48.9 ± 3.4	0.01
MVA(sq.cm)	1.2 ± 0.34	0.9 ± 0.26	0.001
LAAEV(cm/sec)	29.5 ± 5.8	14 ± 5.3	<0.001
LAAFV(cm/sec)	33.8 ± 5.2	22 ± 4.5	<0.001
LSV(cm/sec)	12.4 ± 1.8	8.4 ± 1.4	<0.001
LDV(cm/sec)	11.7 ± 1.2	7.5 ± 2.0	<0.001
Thrombus	5(12)	4(57)	<0.001
SEC	19(46)	7(100)	<0.001


60
50
40
30
20
10
0
AF
EF
LA D
MVA
Without embolic events
With embolic events


35
30
25
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LAAEV
LAAFV
LSV
LDV
Without embolic events
With embolic events

Comparison of Patients with and without Thromboembolic Events

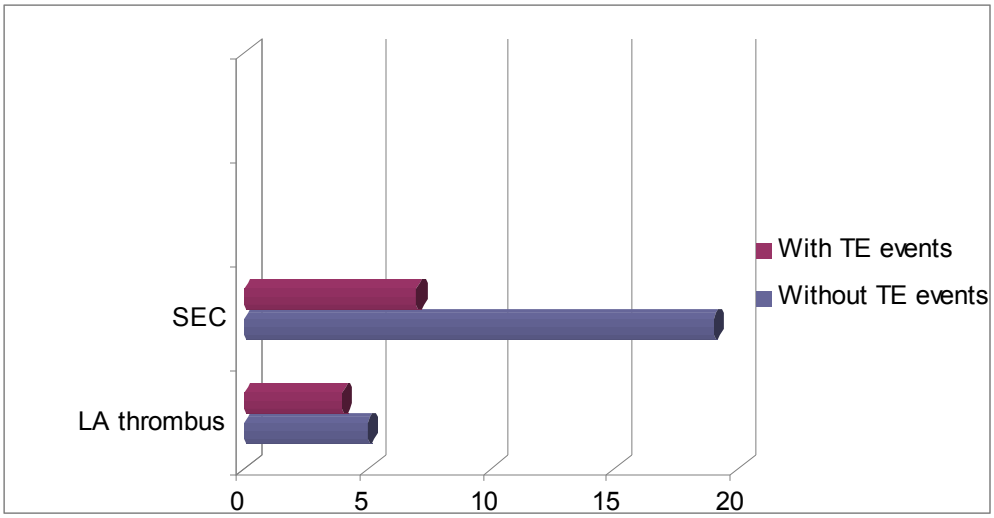

Table-4. The independent determinants of thromboembolic events

Variables	*P*	*Odds ratio*	*95% CI*
Age	0.2	1.2	0.94-1.47
AF	0.3	1.9	0.74-13.03
EF	0.7	0.9	0.62-1.27
LA dimension	0.5	1.03	0.87-1.22
MVA	0.1	0.01	0.00-4.34
SEC	0.01	2.7	1.26-16.85
Thrombus	0.4	2.1	0.61-10.71
LAAEV	0.08	0.7	0.41-1.94
LAAFV	0.1	0.8	0.61-1.24
LSV	0.003	0.2	0.08-0.58
LDV	0.2	0.7	0.54-1.32

The patients with thromboembolic events were older and had a higher incidence of AF, lower EF, larger LA size, and smaller MVA.They also had significantly higher incidence of SEC and thrombus and a lower LAAEV, LAAFV, LSV and LDV .LAA function is more depressed among patients with embolic events. Multivariate logistic regression analysis showed that LSV and the presence of SEC were independently associated with thromboembolic events.

ROC curve analysis was performed to evaluate the clinical usefulness of LAAEV and LSV for discrimination between patients with and without thrombo embolic events .The area under the curve was higher for LSV than LAAEV. The cutoff value of LSV was 7.0 cm/s for the patients with thrombo embolic events with a sensitivity of 95.0% and a specificity of 91.2%.

DISCUSSION

Thromboembolic events are the most important complications in patients with MS .The incidence vary from 10% to 20%. The LAA is the commonest site of thrombus formation in MS .LAA is a highly dynamic structure and prevents stasis in healthy subjects, but when the LAA function impairs, stasis increases, which leads to formation of SEC and /or thrombus. However, LAA dysfunction is one of the most important risk factors for systemic embolization.

Today Doppler transesophageal echocardiography is mostly used to assess the LAA function. LAAEV by PWD reflects the LAA function and the value of LAAEV < 25 cm is generally accepted as a LAA dysfunction. However the measurement of LAAEV is an indirect sign of LAA contraction and influenced by different extrinsic factors, such as left atrial volume, pulmonary venous flow, the left ventricular diastolic filling properties, and LAA size and morphology. Hoit et al also reported that the magnitude and pattern of LAA flow velocities are dependent on acute changes in loading conditions.One of the most important findings of LAA dysfunction is the presence of SEC.

Previous studies showed that some patients have LAA dysfunction and an increased risk of SEC and thrombus formation independent of low velocities detected by standard Doppler. Daimee et al found that 23% of the patients with normal LAA function(LAAEV>25 cm/s) had SEC and 46% of patients with LAA dysfunction(LAAEV <25 cm/s) had no SEC.In our study,SEC was found in 29.0% of the patients with LAAEV > 25 cm/s,whereas it was not detected in 31.3% of the patients with LAAEV < 25 cm/s.Beside,on these findings,LAAEV may not accurately reflect the LAA function.So the additional parameters are needed for accurate assessment of LAA function.

Myocardial velocities obtained by TDI are less dependent on preload and recent studies showed that the LAA contractile functions can be evaluated by using TDI. LSV and LDV correspond with active LAA contraction and relaxation,respectively. Eryol et al reported that the decreased LSV was an independent predictor of an impaired LAA systolic function in patients with MS.They suggested that LSV provides a reproducible parameter for quantification of LAA systolic function.One of the most important findings of LAA systolic dysfunction is the presence of SEC .Ozer et al demonstrated that LSV was a better predictor of SEC than LAAEV in nonvalvular AF. In our study,LSV was significantly reduced in patients compared to the controls and strongly correlated with the density of SEC,whereas,LAAEV was weakly correlated with the density of SEC.

Accurate evaluation of Left Atrial Appendage function can provide better thromboembolic risk estimation and opportunity of treatment,such as anticoagulant therapy.Previous studies suggested that standard Doppler method had a potential limitation in predicting the risk of thromboembolism.But the relation between LAA tissue velocities and thromboembolic events has not been clearly shown.In our study,multivariate regression analysis showed that LSV was independently associated with thromboembolic events.The cutoff value of LSV obtained by ROC curve analysis was 7.0 cm/s for patients with thromboembolic events with a sensitivity of 95.0% and a specificity of 91.2%.

CONCLUSION

- Left Atrial Appendage function is depressed in patients with mitral stenosis as assessed by Left Atrial Appendage late peak Emptying Velocity and Left Atrial Appendage late peak Systolic velocity.
- The deterioration of Left Atrial Appendage function is more prominent among patients with Atrial fibrillation and those with embolic events.
- Left Atrial Appendage late peak Systolic velocity as assessed by Tissue Doppler imaging seems to be more reliable than Left Atrial Appendage late peak Emptying Velocity assessed with Pulse Doppler imaging in assessing Left Atrial Appendage function.
- Left Atrial Appendage late peak Systolic velocity is a useful parameter in evaluating Left Atrial Appendage function in patients with mitral stenosis.

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GLOSSARY AND ACRONYMS

TEE- Trans esophageal echocardiogram.
TTE- Trans thoracic echocardiogram.
LAAEV-Left Atrial Appendage late peak Emptying Velocity
LAAFV -Left Atrial Appendage late peak Filling Velocity
LSV-Left Atrial Appendage late peak Systolic velocity
LDV- Left Atrial Appendage late peak Diastolic velocity
LAASEC-Left atrial appendage spontaneous echo contrast
TDI - Tissue Doppler imaging .
TEE-Transesophageal echocardiography .
LA = Left atrial;
LVEDV = Left ventricular end-diastolic volume;
LVESV = Left ventricular end-systolic volume;